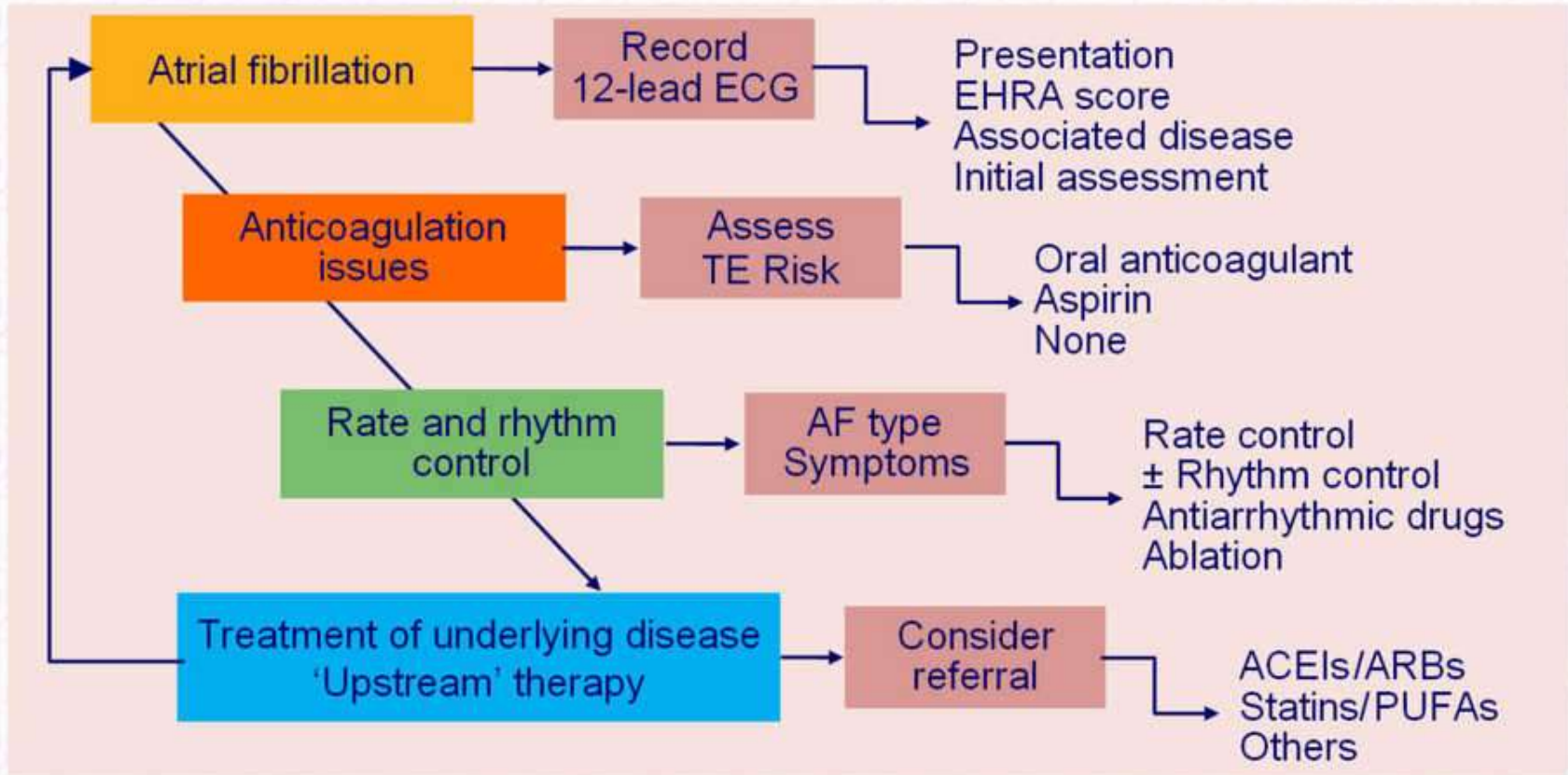


# Atrial Fibrillation

Professor Ralph Stewart

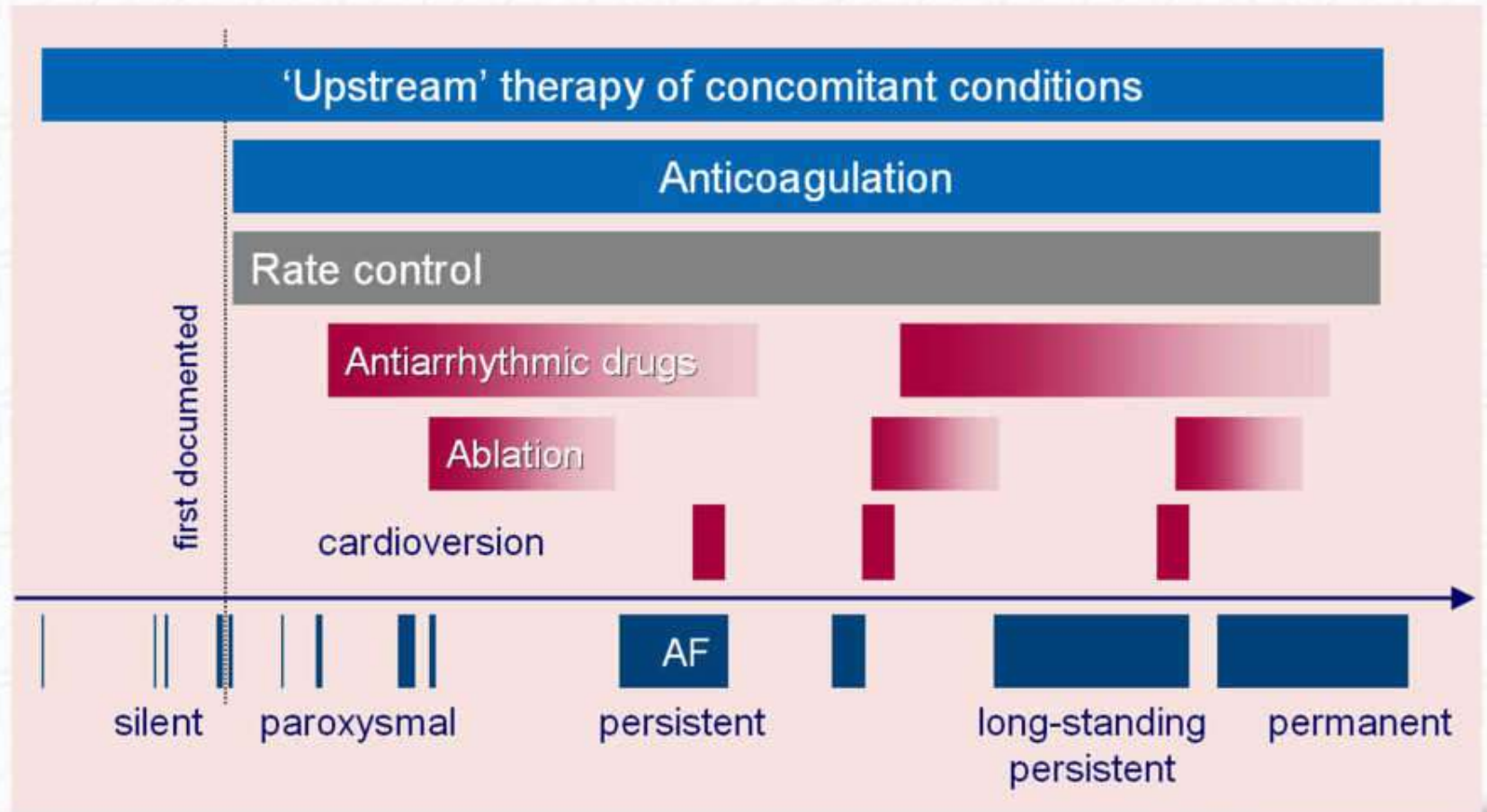
Auckland Heart Group  
General Practitioner Update  
August 2011

# The management cascade for patients with AF



ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; PUFA = polyunsaturated fatty acid; TE = thrombo-embolism.

# Natural time course of AF



AF = atrial fibrillation

# General Management of the AF Patient

**Clinical management of patients with AF involves the following five objectives:**

1. Prevention of thromboembolism
2. Optimal management of concomitant cardiovascular disease
3. Symptom relief
4. Rate control
5. Correction of the rhythm disturbance





# Atrial Fibrillation

## A Substantial Threat to the Brain

- ▶ 5%/year stroke rate
- ▶ 12%/year for those with prior stroke
- ▶ AF-related strokes have worse outcomes



# Risk of stroke in AF

## High-Risk Factors

- ▶ Mitral stenosis
- ▶ Prosthetic heart valve
- ▶ History of stroke or TIA

## Moderate-Risk Factors

- ▶ Age >75 years
- ▶ Hypertension
- ▶ Diabetes mellitus
- ▶ Heart failure or ↓ LV function



# The CHADS<sub>2</sub> Index

## Stroke Risk Score for Atrial Fibrillation

	<u>Score (points)</u>	<u>Prevalence (%)*</u>
Congestive Heart failure	1	32
Hypertension	1	65
Age >75 years	1	28
Diabetes mellitus	1	18
Stroke or TIA	2	10
Moderate-High risk	<u>≥2</u>	50-60
Low risk	0-1	40-50

VanWalraven C, et al. *Arch Intern Med* 2003; 163:936.

\* Nieuwlaat R, et al. (EuroHeart survey) *Eur Heart J* 2006 (E-published).



# The CHADS<sub>2</sub> Index

## Stroke Risk Score for Atrial Fibrillation

	<u>Score</u> <u>(points)</u>	<u>Risk of Stroke</u> <u>(%/year)</u>	
	0	1.9	
	1	2.8	
Approximate Risk threshold for Anticoagulation	.....	.....	3%/year
	2	4.0	
	3	5.9	
	4	8.5	
	5	12.5	
	6	18.2	

Van Walraven C, et al. *Arch Intern Med* 2003; 163:936.  
Go A, et al. *JAMA* 2003; 290: 2685.  
Gage BF, et al. *Circulation* 2004; 110: 2287.



# Natural History of “Lone” Atrial Fibrillation

*No Cardiopulmonary Disease; <60 Years Old*

97 Patients  
Mean Age = 44

14.8 years  
Follow-up

0.35%/yr Stroke  
0.40%/yr Mortality



# Risk Stratification and Anticoagulation

## Stroke Reduction with Warfarin Instead of Aspirin

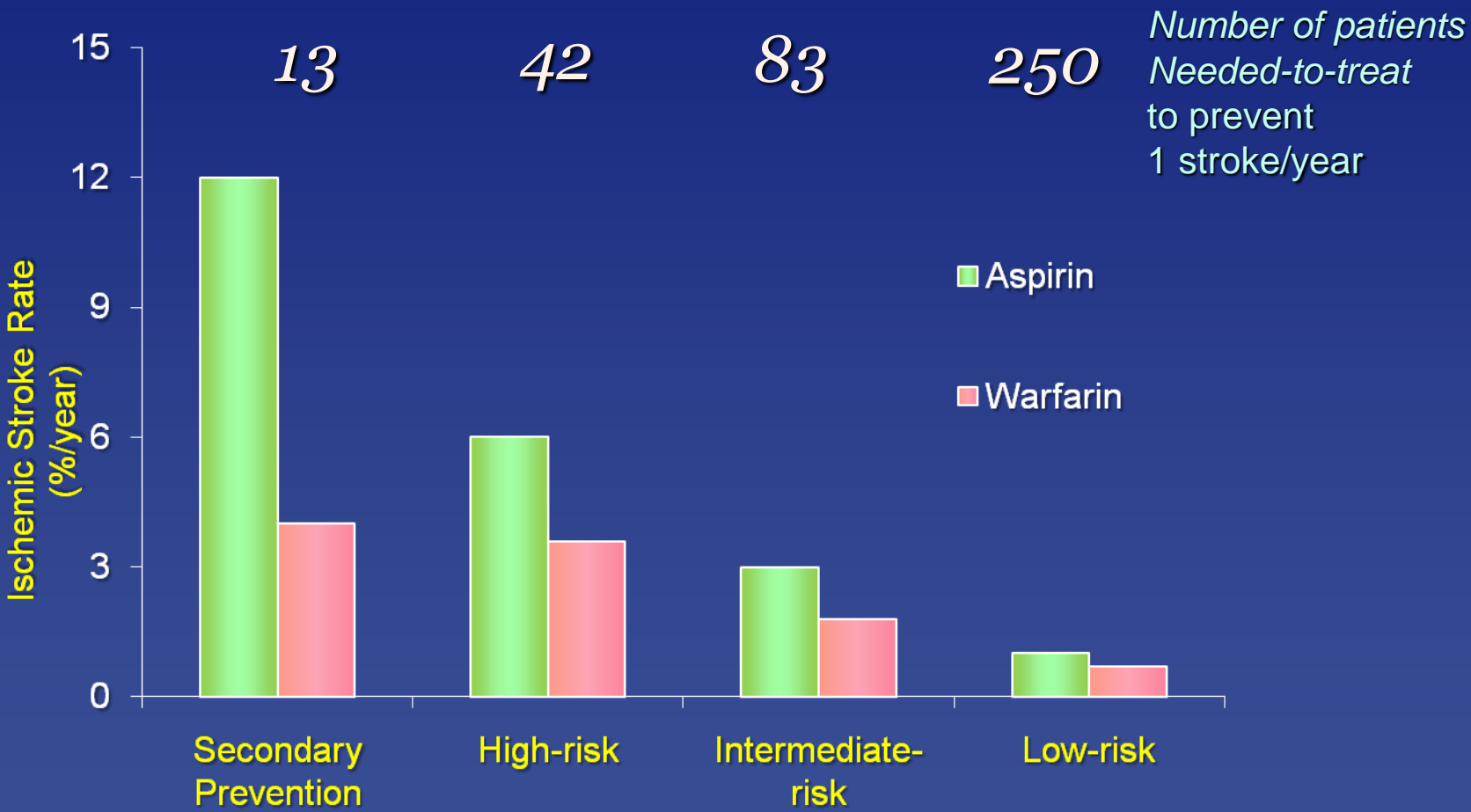
CHADS<sub>2</sub> Score

3

2

1

0



EAFST Study Group. *Lancet* 1993; 324:1255.  
Zabalgoitia M, et al. *J Am Coll Cardiol* 1998; 31:1622.

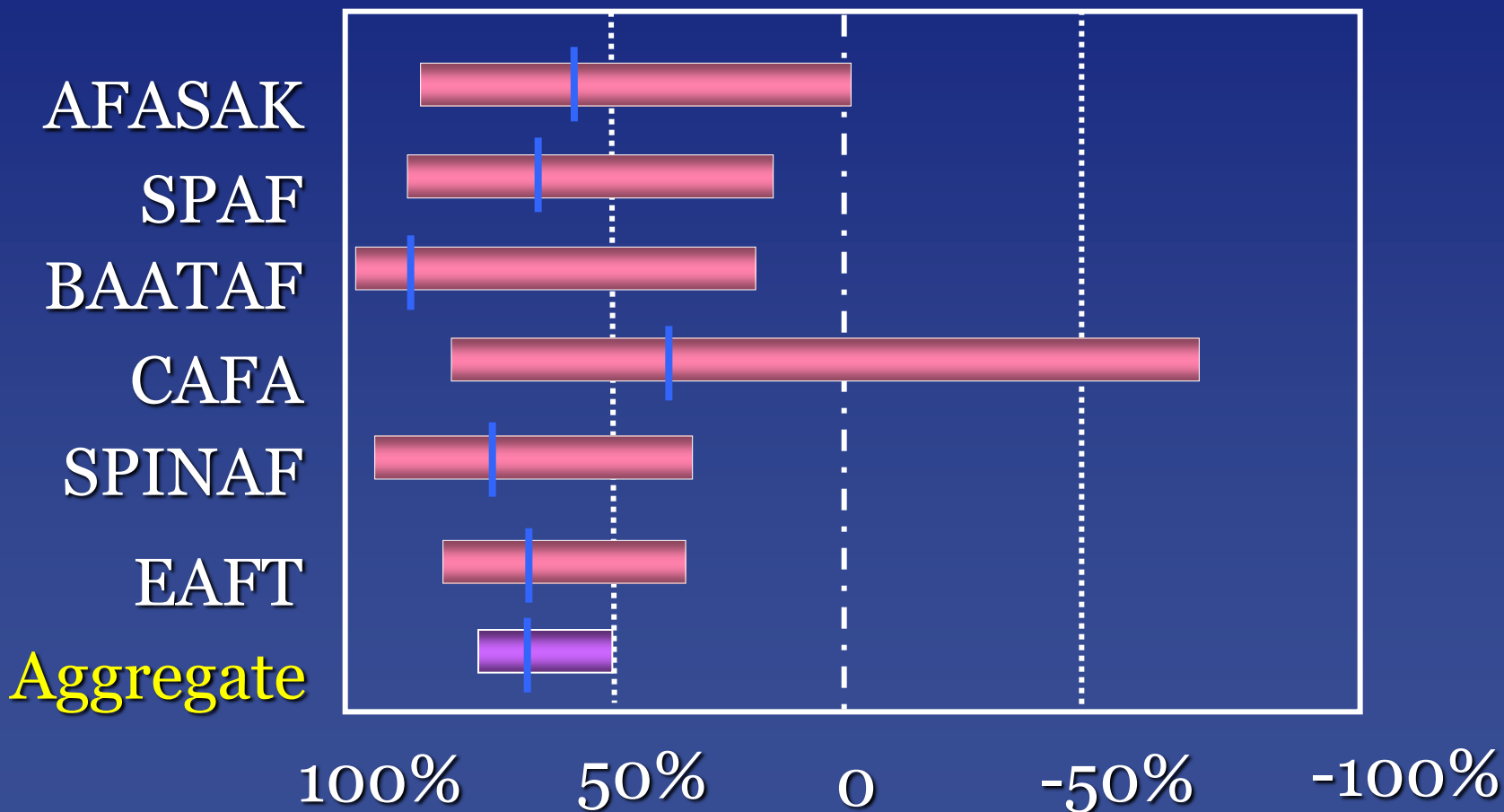


# Anticoagulation in Atrial Fibrillation

## Stroke Risk Reductions

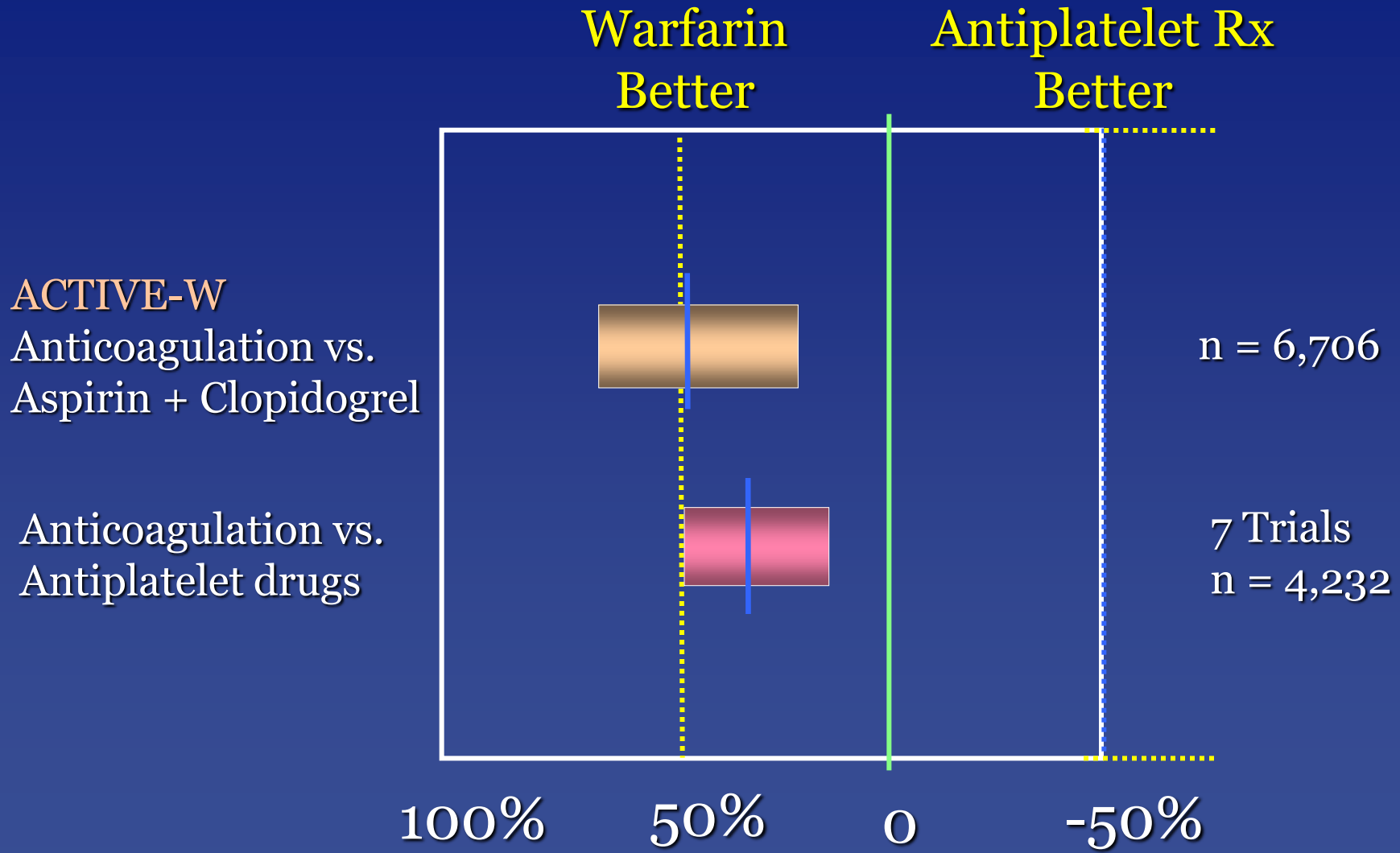
Warfarin  
Better

Control  
Better





# Reduction in Risk of Stroke with Different Anti-thrombotic Therapy for Atrial Fibrillation

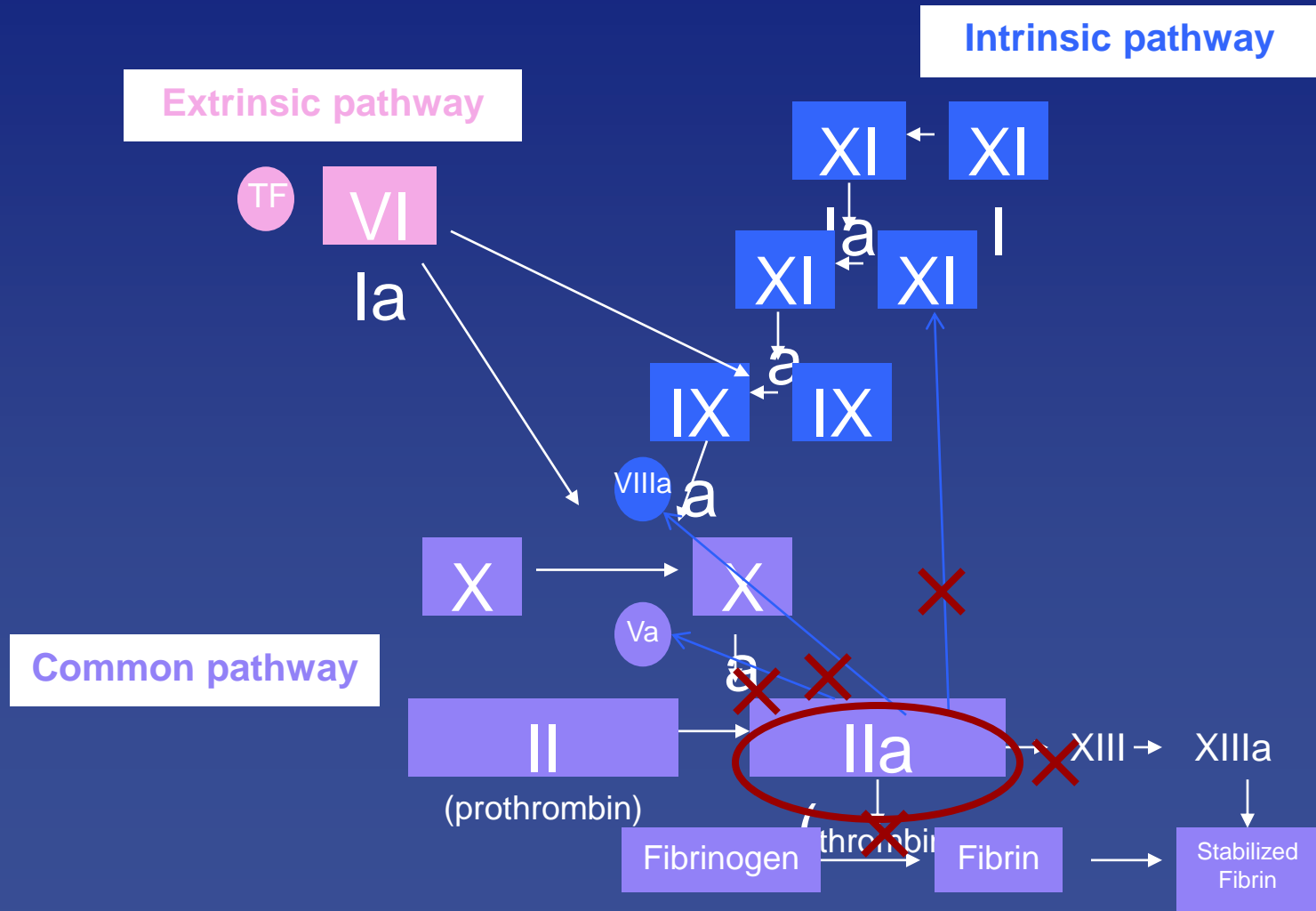


Connolly S, et al. *Lancet* 2006; 367:1903.  
Hart R, et al. *Ann Intern Med* 2007;146:857.



# Dabigatran / Pradaxa

## Oral Direct Thrombin Inhibitor





# The RE-LY Trial

## Warfarin vs Dabigatran in high risk AF

- Atrial Fibrillation with  $\geq 1$  Risk Factor
- Absence of Contraindications

**R**

**Blinded Event Adjudication**

**Open**

**Blinded**

**Warfarin  
Adjusted  
INR 2.0 – 3.0  
N=6000**

**Dabigatran  
etexilate  
110 mg BID  
N=6000**

**Dabigatran  
etexilate  
150 mg BID  
N=6000**

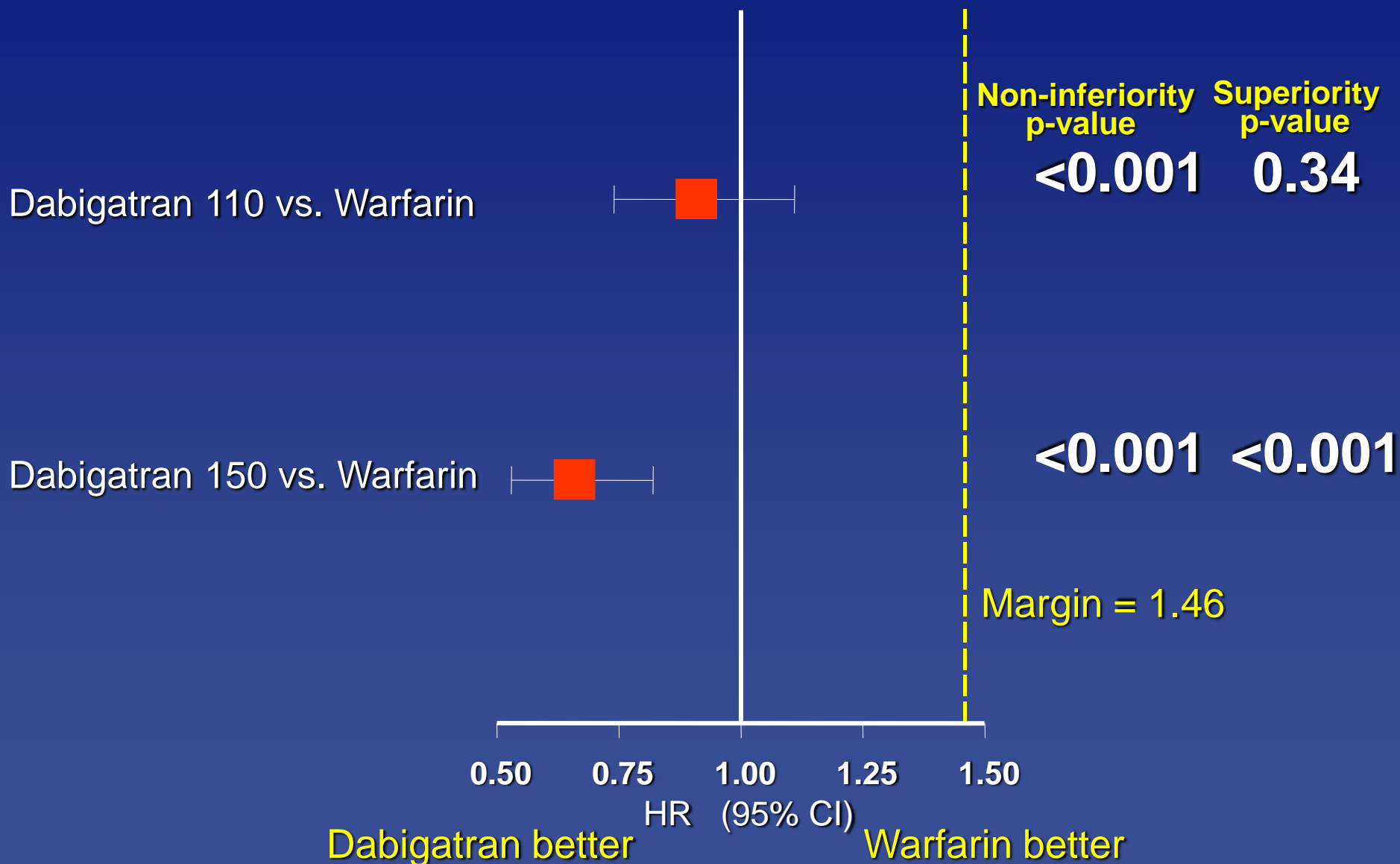


# RE-LY: Baseline Characteristics

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

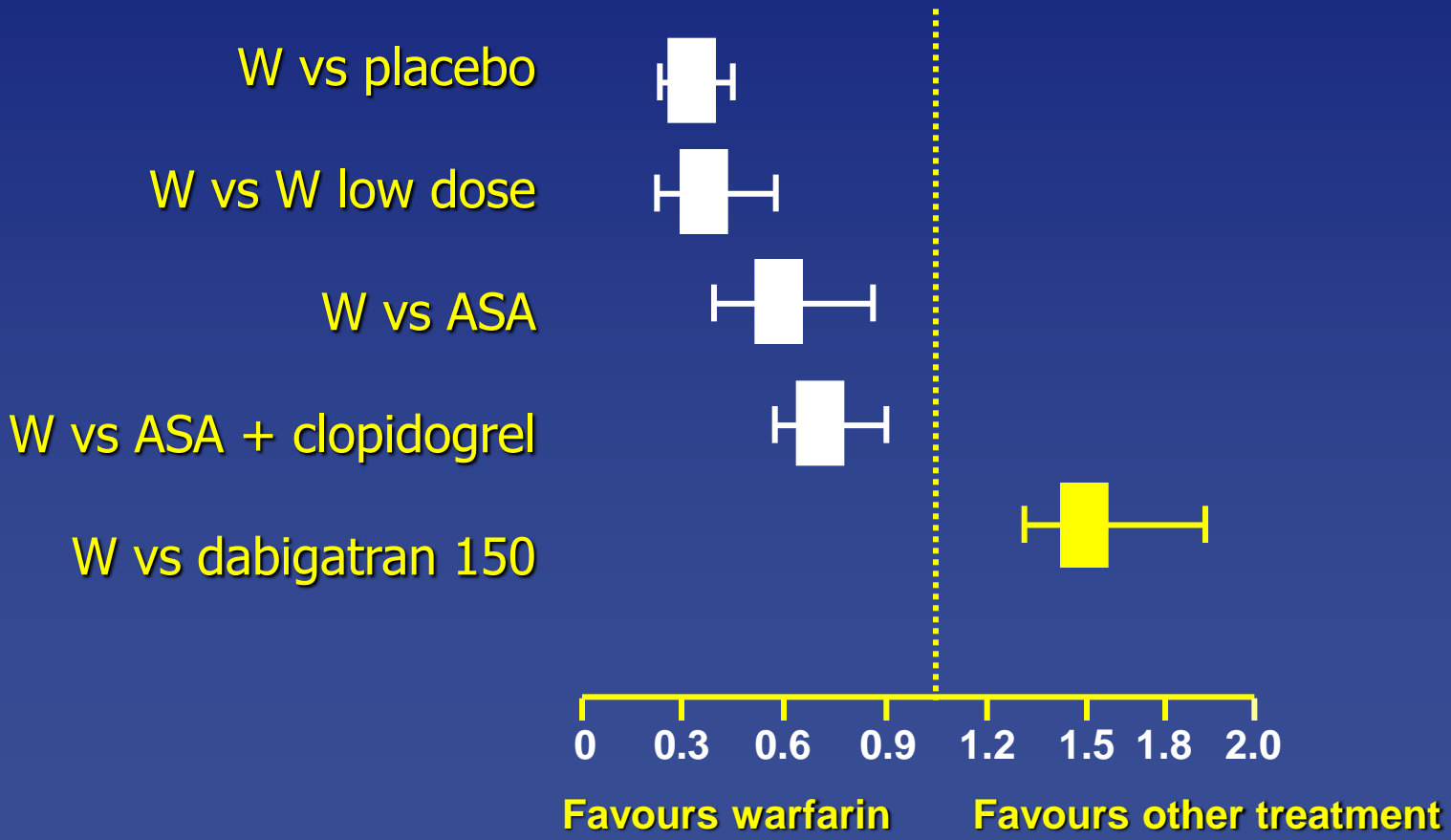


# RE-LY: Stroke or Systemic Embolism





# Clinical trials of Anti-thrombotic Treatments for Prevention of Ischemic Stroke in AF





# RE-LY: Outcomes in Secondary-Prevention Patients with AF by Treatment Assignment

End point	Warfarin	Dabigatran 110 mg twice daily	RR (95% CI) vs warfarin	p	Dabigatran 150 mg twice daily	RR (95% CI) vs warfarin	p
Stroke/ systemic embolism (%/year)	2.74	2.32	0.85 (0.59–1.22)	0.37	2.07	0.76 (0.53–1.10)	0.14
Hemorrhagic stroke (n)	18	2	0.11 (0.03–0.47)	0.003	5	0.27 (0.10–0.72)	0.009
ICH (n)	30	6	0.20 (0.08–0.47)	0.001	13	0.41 (0.21–0.79)	0.007

Diener HC et al. American Stroke Association International Stroke Conference 2010; February 26, 2010; San Antonio, TX.



# RE-LY: Secondary Efficacy Outcomes According to Treatment Group

Event	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Myocardial infarction	0.7%	0.7%	0.5%
Vascular death	2.4%	2.3%	2.7%
All-cause mortality	3.8%	3.6%	4.1%



# RE-LY: Annual Rates of Bleeding

	Dabigatran 110mg	Dabigatran 150mg	Warfarin	Dabigatran 110mg vs. Warfarin		Dabigatran 150mg vs. Warfarin	
n	6015	6078	6022	RR 95% CI	p	RR 95% CI	p
Total	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life- Threatening	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Gastro- intestinal	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

# Key bleeding risk factors

Age > 75 years, frailty, co-morbidity

On anti-platelet

Renal impairment

Use of NSAID

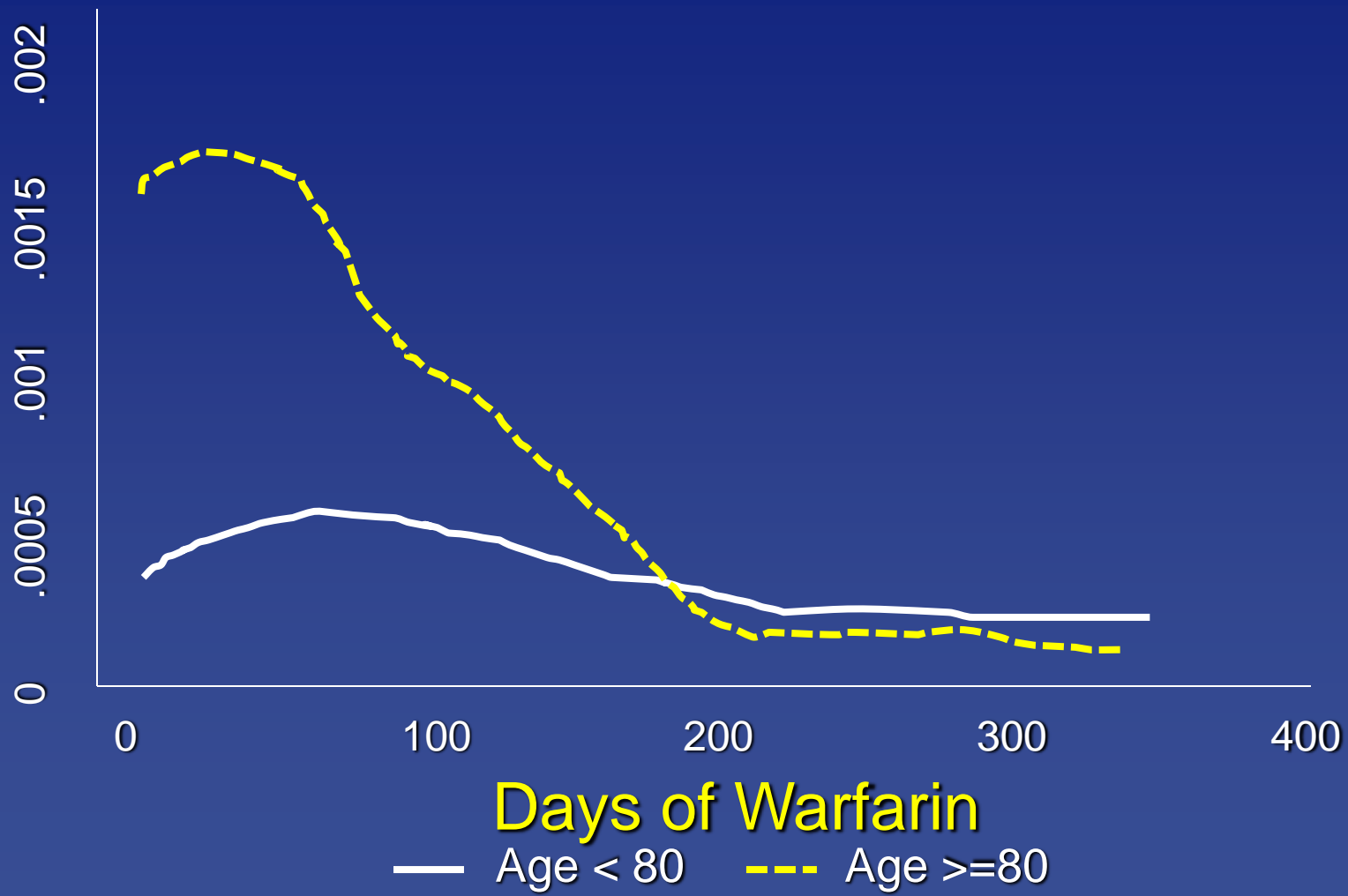
Clinically important bleeding history (eg GI haemorrhage)

Labile INR's on warfarin



# Risk of Stopping Therapy in the First Year Among Patients Newly Starting Warfarin by Age

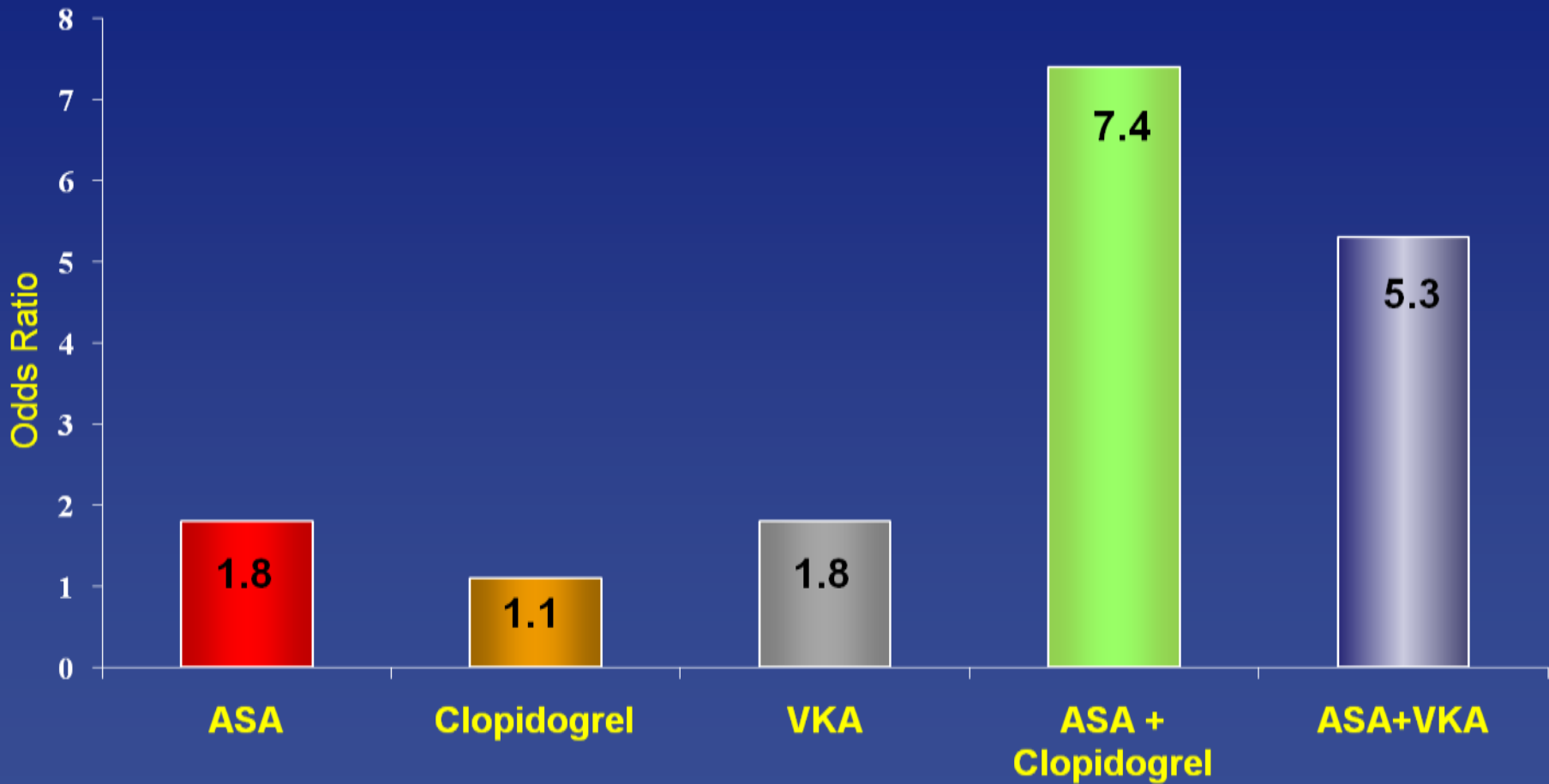
Risk of Stopping Warfarin



Hylek EM et al, *Circulation* 2007;115(21):2689-2696.



# Risk of GI bleeding with Different Anti-thrombotic Agents



Mean age=72 years

# Low does aspirin compared to placebo for primary prevention of vascular disease

Absolute reduction = 0.06% per year  
(12%PR = 0.06%AR )

Primary prevention trials with 95000 individuals &  
3554 serious vascular events

Anti-Thrombotic Trialist Collaboration  
Lancet 2009

# Anti-coagulation and anti-platelet treatment: Consider strength of indication and bleeding risk

	<b>Anti-coagulation</b>	<b>Anti-platelet</b>
<b><i>Weak indication</i></b>	Atrial fibrillation but no risk factors for stroke	CV risk factors but no clinical evidence of CVD
<b><i>Usually indicated</i></b>	Atrial fibrillation and risk factors for stroke	Stable coronary artery or cerebro-vascular disease
<b><i>Strong indication</i></b>	Atrial fibrillation and previous stroke / TIA.  Mechanical heart valve	Coronary stent < 6 months Drug eluting stent <12 months Acute coronary syndrome or carotid territory stroke/TIA < 6mths Advanced CVD / history of multiple events



# Which Dose of Dabigtran ?

## Lower-dose regimen (110mg bd)

- ▶ Elderly
- ▶ Renal insufficiency
- ▶ Lower stroke risk (CHADS<sub>2</sub> score of 1)
- ▶ Increased bleeding risk

## Higher-dose regimen (150mg bd)

- ▶ Higher stroke risk (CHADS<sub>2</sub> score  $\geq$  2)